immunodominant epitope sequence] and wherein the peptide comprises less than the sequence of the antigen.

Remarks

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks presented herein, is respectfully requested. Claims 1-2, 4, 6, 9, 11, 13, and 16-17 are amended, and claim 40 is canceled. Claims 1-13, 16-18, 31, and 34-39 are pending. The amendments to the claims are intended to clarify Applicant's invention and not intended to limit the equivalents to which any claim element may be entitled.

The amendments to claims 1 and 17 are supported by originally-filed claims 1, 13 and 17, and by the specification at page 16, lines 9-13, and in Example II of the specification.

The amendments to claim 2 is supported by originally-filed claim 2 and at page 16, lines 9-13 of the specification.

Amended claims 4, 6, 9, 11, 13, and 16 are supported by originally-filed claims 4, 6, 9, 11, 13, and 16, respectively.

With respect to items 1 and 6 of the Office Action, the Examiner is requested to note that in the Amendment filed on August 17, 1999, Applicant amended the specification to delete the "Cross-Reference to Related Application" section of the specification.

With respect to item 3 of the Office Action, the Examiner is requested to consider that claim 39 is dependent on the elected claims, i.e., claim 39 is dependent on claims 1, 2 and 17, and claim 40 is canceled. Therefore, claim 39 is directed to an elected invention and so should not be withdrawn from consideration under 37 C.F.R. 1.142(b).

The 35 U.S.C. § 102(b) rejections

The Examiner rejected claims 1-3, 6, 8-9, 17-18, 31, 34, and 37 under 35 U.S.C. § 102(b) as being anticipated by Hoyne et al. (J. Exp. Med., 178, 1783 (1993)). The Examiner also rejected claims 1-5, 8 and 11-13 under 35 U.S.C. § 102(b) as being anticipated by WO 94/00148. As these rejections may be maintained with respect to the pending claims, they are respectfully traversed.

Hoyne et al. disclose the administration by inhalation of a peptide having amino acid residues 111-139 of Der p1, a house dust mite allergen, to naive and primed C57BL/6 (inbred) mice which are high responders to Der p1. The authors disclose that residues 111-139 were chosen for study because they represent a major T cell epitope recognized by human Der p1-specific T cell clones (Hoyne et al. citing to Higgins et al., J. Allergy Clin. Immunol., 90, 749, (1992), a copy of which is enclosed herewith). However, the results described in Higgins et al. were not obtained from a population of T cells, or a set of independent T cell clones, but rather from one particular human T cell clone (KS2.12) which was selected for reactivity to peptide 101-119. Higgins et al. report that pretreatment of the KS2.12 cells with the peptide rendered them unresponsive to challenge with Der p1, as measured by a proliferation assay. Thus, Higgins et al. do not provide evidence that Der p1 peptide 101-119 comprises a universal T cell epitope, i.e., one recognized by mammals, or cells from mammals, of differing immune response haplotypes.

Hoyne et al. report that when a population of lymph node T cells isolated from tolerant C57BL/6 mice, i.e., mice which were unresponsive to Der p1 challenge, were restimulated *in vitro* with Der p1, the T cells secreted very low levels of interleukin-2, proliferated poorly, and were unable to provide cognate help to stimulate specific antibody production *in vitro* (abstract). It is also disclosed that intranasal peptide therapy inhibited an ongoing immune response to the allergen (abstract).

While the authors of Hoyne et al. speculate that their studies indicate that administering immunogenic peptides intranasally may be an effective way to control aberrant immune responses in humans (page 1784), the results of those studies were obtained from one strain of inbred mice selected as having a profound response to Der pl, and so cannot be readily extrapolated to the response in mammals that are divergent at their immune response loci (for example, see WO 94/00148, discussed below, which indicates that the *in vitro* results in murine immune cells do not necessarily correlate to the *in vitro* results in human immune cells, and the human results reported in Norman et al., discussed below, which were in contrast to reported results from mice).

Moreover, in concluding, Hoyne et al. admit that they "cannot exclude other regulatory mechanisms operating within the lung that may be active in modulating the response

antigen-reactive T cells" (page 1787). For example, Hoyne et al. mention that $CD8^+$ suppressor cells may have a role in immune tolerance after antigen inhalation in rats (page 1787). Further, the Hoyne et al. article fails to disclose whether peptide 101-119 administration altered antibody production *in vivo*.

Thus, Hoyne et al. do not disclose or suggest the use of a universal peptide epitope to suppress, tolerize or inhibit the priming or activity of $CD4^+$ T cells which are associated with antibody production (claims 2 and 17). Nor does Hoyne et al. teach or suggest the use of a universal peptide epitope to prevent or inhibit aberrant, pathogenic or undesirable antibody production which is specific for a particular endogenous antigen in a human (claim 1). Hence, Hoyne et al. do not anticipate Applicant's invention.

Therefore, withdrawal of the rejection of claims 1-3, 6, 8-9, 17-18, 31, 34, and 37 under 35 U.S.C. § 102(b) over Hoyne et al. is respectfully requested.

To prepare peptides that bind to MHC gene products but do not activate T cells, WO 94/00148 discloses the preparation of synthetic peptide analogs of myasthogenic T cell epitopes from amino acid residues 195-212 or amino acid residues 259-271 of the human acetylcholine receptor (AChR) α subunit. T cell lines specific for a peptide having residues 259-271 (p259-271) and a peptide having residues 195-212 (p195-212) were developed (those lines are referred to as TCBALB/c259-271 and TCSJL195-212, respectively). Substituted peptides p305 (a peptide having a Ser→Asp substitution at position 266) and p307 (a peptide having a Glu→Asp substitution at position 262) triggered low proliferative responses in the T cell line TCBALB/c259-271, while p306 (having a Glu→Lys substitution at position 262) did not (page 16, lines 22-26; (Figure 1). Substituted peptide p455 (having a Met→Ala substitution at position 207) did not stimulate the proliferation of TCSJL195-212 cells (Example 5).

The T cell line TCBALB/c259-271 was incubated with irradiated syngeneic spleen cells and antigen presenting cells (APCs) in the presence of increasing doses of three analogs, p305, p306 and p307, and a fixed dose of p259-271 (Example 2). As shown in Figure 2, p306 inhibited the proliferative response of the T cell line TCBALB/c259-271 to p259-271, while p307 inhibited proliferation minimally and p305 did not inhibit proliferation at all. p307 and p305 also led to the production of antibodies when mixed with spleen cells from BALB/c mice immunized with p259-271, normal syngeneic spleen cells and T cell line TCBALB/c259-

271. In contrast, it is disclosed that p306 inhibited anti-p259-271 antibody production (page 18).

It is also disclosed that BALB/c mice were immunized with p259-271 (the route of administration is not specified), lymph node cells collected, and the response of the cells to the analogs in the presence of p259-271 determined. p305 and p307 elicited low proliferative responses, while p306 did not. Thus, of the four peptide analogs tested, only p306 and p455 failed to stimulate the proliferation of a peptide-specific T cell line or lymph node cells from immunized mice, or to stimulate antibody production from the cell line.

Example 6 of WO 94/00148 describes that the peripheral blood lymphocytes (PBLs) from three myasthenia gravis (MG) patients were contacted with p195-212, p195-212 and p455, p455, and p259-271 and p305, p306 or p307. The proliferative response of PBLs of all three patients was inhibited by p455 (77-100% inhibited), p307 (65-78% inhibited) and p305 (34-85% inhibited), while the proliferative response of PBLs from 2/3 MG patients was inhibited by p306 (71-100% inhibited). Nonetheless, these results may indicate that the analog competes for or otherwise inhibits the binding of p195-212 or p259-271 to the restriction element recognized by p195-212 or p259-271 in MG PBLs. The data in Figure 4 indicates that p306 competes with p259-271 for binding to TCBALB/c259-271. Moreover, WO 94/00148 does not disclose whether the peptide analogs inhibited antibody production from the MG PBLs.

It is of interest to note the *in vitro* and *in vivo* results for the peptide analogs in inbred mice were not necessarily predictive of *in vitro* results in human PBLs, i.e., p305 and p307 did not substantially inhibit the proliferation of a peptide-specific murine T cell line or murine lymph node cells from peptide-immunized mice immunized, but did inhibit the proliferative response of PBLs from MG patients. In this regard, the Examiner is requested to recall that Moiola et al. (J. Immunol., 152, 4686 (1994), of record) admit that the "large number of AChR sequences forming CD4+ epitopes in MG patients casts some doubts about the feasibility of similar immunosuppressive approaches in this disease" (page 4696). This reference also indicates that the epitope repertoire of Th cells involved in the synthesis of pathogenic antibodies may be more limited than that detected by testing CD4+ cell proliferation *in vitro* (page 4697).

Thus, data from inbred mice or a population of cells which include $CD4^+$ and $CD8^+$ cells, e.g., MG PBLs, does not provide a basis for concluding that the administration of a

peptide comprising a universal epitope is useful to suppress, tolerize or inhibit the priming or activity of $CD4^+$ T cells which are associated with antibody production (claim 2) or to prevent or inhibit aberrant, pathogenic, or undesirable antibody production in a human (claim 1).

Thus, WO 94/00148 does not anticipate Applicant's invention. Hence, withdrawal of the rejection of claims 1-5, 8 and 11-13 under 35 U.S.C. § 102(b) over WO 94/00148 is respectfully requested.

The 35 U.S.C. § 103 rejections

The Examiner rejected claims 1, 2 and 16 under 35 U.S.C. § 103 as being unpatentable over Hoyne et al. in view of Norman et al. (Am. J. Respir. Crit. Care Med., 154, 1623 (1996)). The Examiner also rejected claims 1, 3, 6-10, 34, and 37-38 under 35 U.S.C. § 103 as being unpatentable over Hoyne et al. in view of Kurup et al. (Peptides, 17, 183 (1996)). The Examiner further rejected claims 34-36 under 35 U.S.C. § 103 as being unpatentable over Hoyne et al. in view of Zimmerman et al. (U.S. Patent No. 4,649,132). As these rejections may be maintained with respect to the pending claims, they are respectfully traversed.

As discussed above, Hoyne et al. do not disclose or suggest the use of a universal epitope peptide to suppress, tolerize or inhibit the priming or activity of $CD4^+$ T cells which are associated with antibody production, in mammals having divergent immune response loci, or the use of such a peptide to alter aberrant, pathogenic or undesirable antibody production specific for a particular endogenous antigen in humans, as their reported results were obtained from inbred mice and a population of cells, i.e., lymph node cells. Thus, Applicant's invention is not obvious in view of Hoyne et al.

In the introduction of Norman et al., the authors relate that T cells and antibodies interact with different ligands on allergens (page 1623). For example, IgE antibodies attach to complex B cell epitopes that require intact tertiary structures, while T cell receptors respond to short peptides from the allergen embedded in the surface of mixed histocompatibility molecules on antigen presenting cells (page 1623). The authors suggest that in patients who are allergic to cats, T cell non-responsiveness might be induced by peptides representing T cell epitopes of allergens, although the authors caution that the peptides must be carefully selected to avoid peptides having tertiary structures recognized by IgE antibodies (page 1623).

To determine whether peptides having T cell epitopes can induce tolerance, humans known to be allergic to cats were subcutaneously injected with a combination of two T cell reactive peptides of Fel d 1, the principle allergen of cat dander. The two peptides, IPC-1 (corresponding to residues 7-33 of chain 1 of Fel d 1), and IPC-2 (corresponding to residues 29-55 of chain 1 of Fel d 1), had been characterized as having multiple dominant T cell epitopes (Norman et al citing to Cornell et al., J Allergy Clin. Immunol., 98, 884 (1996)) and Briner et al. (Proc Natl. Acad. Sci. USA, 90, 7608 (1993)).

Briner et al. reported results obtained from the subcutaneous administration of a number of Fel d 1 peptides, including IPC-1 and IPC-2, to $B6D_2F_1(H\text{-}2^{bxd})$ and $B6CBAF_1(H\text{-}2^{bxa})$ mice. Of interest is that Briner et al. do not disclose any experiments in which the immune response to the peptides for the two strains is compared and so this reference provides no evidence that IPC-1 and IPC-2 comprise a universal T cell epitope.

Cornell et al. discloses that Fel-1 (i.e., IPC-1) and /or Fel 2 (i.e., IPC-2) stimulated a T cell response in 95% of T cell lines derived from 53 patients with cat allergy, and suggest that these peptides may be useful in immunotherapy. Although Fel-1 and Fel-2 stimulate the proliferation of T cells the proliferation of T cells, Cornell et al. do not teach or suggest that the administration of Fel-1 and Fel-2 alter aberrant, pathogenic antibody production or provide evidence that the administration of such a peptide to a mammal tolerizes T cells.

Norman et al. disclose that subsequent exposure of the IPC-1 and IPC-2-immunized humans to cats resulted in a decrease in nose and lung symptoms in groups treated with 750 μg or 75 μg of the peptides, but not in the group treated with 7.5 μg of the peptides (Figure 2). However, Norman et al. state that none of the treated groups "showed a significant change in IgE or IgG antibody to Fel d 1" (page 1626, Table 1), and that "T cell proliferation assays to peptides and recombinant Fel d 1 chain 1 and chain 2 did not reveal any consistent alterations attributable to treatment" (page 1626). Clearly, the decrease in nose and lung symptoms in treated patients observed by Norman et al. was not due to inhibition of antibody production or inhibition of T cells. These results were in contrast to the results in Briner et al. (i.e., the subcutaneous administration of a combination of IPC-1 and IPC-2 to mice prior to exposure of Fel d 1 resulted in decreased levels of IL-2 secretion by spleen cells, an indication of

T cell tolerization), leading the authors to admit that the murine model is "in several ways different from human allergy" (page 1628).

Norman et al. do not teach or suggest the administration of peptide to the respiratory tract of a mammal. Moreover, Norman et al. do not teach or suggest that the administration of a particular peptide to a mammal tolerizes T cells, or in any way modulates aberrant, pathogenic or undesirably antibody production in that mammal to an antigen. Hence, Norman et al. do not render Applicant's invention obvious.

With respect to the rejection of claims 1-2 and 16 over the combination of Hoyne et al. and Norman et al., the Examiner asserts that one of ordinary skill in the art would have been motivated to substitute the nasal administration of Hoyne et al. for the subcutaneous administration of Norman et al. as intranasal therapy induces tolerance in naive mice and inhibits T cell function in sensitized mice, and that these two references provide the art worker with a reasonable expectation that peptide therapy would be successful.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to an art worker, to modify the reference or to combine reference teachings so as to arrive at the claimed invention. Second, the art must provide a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. In re Ochiai, 37 U.S.P.Q.2d 1127 (Fed. Cir. 1997); M.P.E.P. §§2142, 2143.

However, the results disclosed in Hoyne et al. were obtained with a population of cells that included $CD8^+$ cells from naive and primed inbred mice immunized with a peptide from an exogenous antigen, the data for which do not evidence that the peptide they employed has a universal epitope. Moreover, the authors admit that $CD8^+$ cells may have a role in immune tolerance, i.e., the presence of $CD8^+$ cells may explain the observed results. As for Norman et al., the subcutaneous administration of a combination of peptides from an exogenous antigen appeared to decrease nose and lung symptoms, but did not effect either antibody synthesis or T cell proliferation. Given that observations in mice and humans relating to peptide therapy can be difficult to reconcile, that peptide therapy for an allergen in humans did not effect antibody production or T cell proliferation in those humans, and that Hoyne et al. do not disclose or suggest which immune cell(s) result in the observed modulating effect, one of ordinary skill in

the art in view of the cited art would have no reasonable expectation that the respiratory administration of a peptide can alter aberrant, pathogenic or undesirable antibody production in humans, or suppress, tolerize, or inhibit $CD4^+$ T cell function in mammals which are divergent at their immune response loci. Thus, the combination of Norman et al. and Hoyne et al. do not render Applicant's invention obvious.

To study the specificity of epitopes of *Aspergillus fumigatus* (Af) antigen that are associated with antibody and cytokine synthesis, Kurup et al. employed five Af peptides to immunize mice of different haplotypes. Four mouse strains, i.e., BALB/c, C57BL/6, AKR, and CBA mice, were immunized by subcutaneous injection with Af peptides from a ribotoxin produced by *Aspergillus restrictus* (a species related to Af). Following immunization, the levels of total serum IgE and *Aspergillus*-specific IgG antibodies were measured. It is disclosed that all four mouse strains showed a slight increase in total serum IgE levels in response to the immunization (page 186). However, these results were variable in that peptide #11 showed a fivefold increase in AKR mice, while the IgE levels of C57BL/6 mice showed no significant increase with any of the peptides. It is also disclosed that peptide-specific IgG antibody responses were also varied among the peptides and mouse strains (page 186). IgG levels in all four strains of mice were higher with peptides #1 and #9, while peptides #5 and #10 resulted in the least antibody response in all four strains (pages 186 and 188). Nevertheless, as shown in Figure 2, with the possible exception of peptide #10 in one strain of mice, the administration of all peptides increased the levels of IgG in immunized mice.

Hence, Kurup et al. do not disclose or suggest a universal epitope peptide or a peptide that is useful to prevent or inhibit aberrant, pathogenic or undesirable antibody production, as all the immunizing peptides increased serum IgE or IgG levels. Nor does Kurup et al. disclose or suggest respiratory administration of a peptide to a mammal. Therefore, Applicant's invention is not rendered obvious by Kurup et al.

With reference to the rejection of claims 1, 3, 6-10, 34, and 37-38 over the combination of Hoyne et al. and Kurup et al., the Examiner asserts that one of ordinary skill in the art would have been motivated to substitute the T cell epitopes derived from Af in Kurup et al. and use them in the intranasal therapy disclosed in Hoyne et al., and that these references provide the art worker with a reasonable expectation that such a therapy would be successful.

However, the Examiner is requested to note that the administration of Af peptides of Kurup et al. actually caused an increase in antibody production and so it is respectfully submitted that one skilled in the art would not be motivated by Kurup et al. to use peptides to treat a mammal with an indication or disease associated with aberrant, pathogenic or undesirable antibody production. Further, Kurup et al. employed a strain of mice that was employed by Hoyne et al., i.e., C57BL/6 mice. Respiratory administration of a peptide from a house dust mite allergen to C57BL/6 decreased *in vitro* antibody production to the allergen (Hoyne et al.) but subcutaneous administration of a fungal peptide related to Af to C57BL/6 mice increased *in vivo* antibody production (Kurup et al.). Therefore, the art worker in possession of Hoyne et al. and Kurup et al. does not have a reasonable expectation that peptide administration could reduce *in vivo* antibody production. See also Norman et al. (none of the peptide-treated groups "showed a significant change in IgE or IgG antibody to Fel d 1", page 1626, Table 1). Hence, the combination of Kurup et al. and Hoyne et al. does not render Applicant's invention obvious.

The '132 patent relates that a fragment of human Factor VIII containing amino acid residues 1690-2332 or 373-740 is immunologically reactive with Factor VIII inhibitors, e.g., these fragments bind Factor VIII inhibitors in plasma obtained from patients known to have Factor VIII inhibitors. However, the '132 patent provides no evidence that the fragments actually bind Factor VIII inhibitors or that administration of these fragments or any other peptide to a mammal would have any beneficial effect, i.e., to prevent or inhibit aberrant, pathogenic, or undesirable antibody production, or inhibit or suppress the activity of $CD4^+$ T cells which are associated with antibody production, in that mammal. Moreover, Factor VIII inhibitors include anti-Factor VIII antibodies. As noted hereinabove, T cells and antibodies recognize different epitopes on an antigen and so the fragments of human factor VIII in the '132 patent are epitopes recognized by antibodies, not T cells. Furthermore, the '132 patent does not disclose or suggest the respiratory administration of a peptide, or a peptide comprising a universal epitope sequence. Hence, Applicant's invention is not rendered obvious by the '132 patent.

With reference to the rejection of claims 34-36 over the combination of Hoyne et al. and the '132 patent, the Examiner asserts that one of ordinary skill in the art would have been motivated to substitute the autoantibody Factor VIII epitopes of the '132 patent and use them in the nasal administration taught by Hoyne et al., and that these two references provide the art

worker with a reasonable expectation that nasal administration of autoantibody Factor VIII epitopes would be effective to prevent or inhibit the aberrant, pathogenic or undesirable antibody production, or suppress, tolerize or inhibit the priming or activity of T cells, in that mammal. Nevertheless, the fact that a fragment of human Factor VIII may react with Factor VIII inhibitors does not provide evidence that administration of these fragments prevents or inhibits antibody production or has an effect on $CD4^+$ T cells. In particular, the administration of those fragments could increase peptide-specific B cell proliferation which would have an adverse effect. Thus, the combination of the '132 patent and Hoyne et al. does not render Applicant's invention obvious.

Therefore, the Examiner is respectfully requested to withdraw the § 103 rejections of the claims.

Conclusion

Applicant believes that the claims are in condition for allowance and respectfully requests reconsideration of the application and allowance of the claims. The Examiner is invited to telephone the below-signed attorney at 612-373-6959 to discuss any questions which may remain with respect to the present application.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Box AF, Assistant Commissioner of Patents, Washington, D.C. 20231 on May 5, 2000.

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